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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/586,486	12/12/2006	Annie Andrieux	128765	4235

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EXAMINER	
CORNET, JEAN P	
ART UNIT	PAPER NUMBER
4121	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/586,486	ANDRIEUX ET AL.	
	Examiner	Art Unit	
	JEAN CORNET	4121	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :06/14/2007, 03/05/2007, 09/07/2006, 07/20/2006.

DETAILED ACTION

1. This application for Patent entered the national stage in the United States of America under U.S.C. 371 from PCT/IB05/00217, filed 01/28/2005, which claiming benefit from European application (EPO) 04290249, filed 01/28/2004. Claims 1-14 are canceled by applicants. Claims 15-24 are pending.

Priority

2. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. All claims receive the benefit of said European application filing date.

Information Disclosure Statement

3. All references submitted on the IDS dated 06/14/2007, 03/05/2007, 09/07/2006 and 07/20/2006 have been considered.

Specification

4. The specification has not been proofed to the extent necessary to uncover the presence of all minor. At this time, applicant's cooperation is requested in correcting any and all errors of which applicant is or may become aware of in the specification.

Election/Restrictions

5. Applicant's election with traverse of Group IV, in the reply filed on 03/20/2009 is acknowledged. The traversal is on the ground(s) that

a. the examiner fails to show the existence of a posteriori by showing the common subject matter does not define a contribution over the prior art and unity did not establish between independent claims.

b. restriction between the Groups I, II, III, IV and V are not in accordance with US practice, because claim 15 which is generic to all claims is only included in Group I, and thus the other Groups II, III, IV and V are each related to the same general formula. An improper assertion of epothilone compound in claim 17 does not define a contribution over the prior art in view of WO 00/66589 and that the assertion is improper because the compound recited in claim 17 is not necessarily common to each of the claims. Restriction requirement also fails to address whether claims 15 defines a contribution over the prior art and does not address the treatment of a neuronal connectivity defect by administering a therapeutic effective amount of an epthilone or derivative thereof., and lastly fails to address how similar the structures are or any reasoning as to why the differences between the structures would have been obvious, herein fails to establish prima facie obvious of invention.

With respect to the requirements to elect a Group, Applicant's arguments are persuasive and the requirements are withdrawn.

c. Restriction between different embodiments (species) of an invention encompassed by a single independent claim is only proper under PCT Rule 13, if the independent claim expressly recites distinct embodiments (such as Markush group) and the requirement that the distinct embodiments share no common subject matter that defines a contribution over the prior art.

This is also found to persuasive because of improper grouping, so election of species within the groups would also be improper, but not because of the applicant's response in part (**c**). However, the election of species requirement is withdrawn. Accordingly, the claims will be searched and examined in their full scope for methods of treating using a therapeutic effective amount of one epothilone or derivatives. .

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 15 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112 first paragraph. Applicant is directed to the Guidelines for the Examination of

Patent Application Under 35 U.S.C. 112 First "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claim is drawn to a method of treating neuronal connectivity defects using an effective amount of epothilone or derivative thereof.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus …") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although

the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163.

Applicant provides no description of the claimed derivatives thereof either in words, by structure, by chemical name, or by physical properties that would indicate that the Applicant was in possession of the claimed derivative thereof at the time of the invention.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed derivatives thereof. A review of the language of the claim 15 is an extremely broad term encompassing at least billions of possible different compounds; while

there are a few claimed compounds present (for which it is not clear whether these are "epothilones" or "derivatives of epothilones" or both),

. One or ordinary skill in the art would not recognize from the disclosure that the applicant was in possession of the metabolite./ The specification does not clearly allow person of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Limitation of “about 0.01Kg/dose to about 100mg/Kg/dose” in claim 23 renders the claim unclear because the metes and bound of the claim cannot be determined. And the limitation of “in particular epothilone D” in claim 21 renders the claim unclear whether the subject matter following the phrase further limits the claim, or has no meaning in the claim; that is the metes and bound of the claim cannot be determined.

Claims 18 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The limitation 'the epothilone is a derivative" is unclear as to whether or not the group of compounds emcompass other derivatives in addition to the compound of formula II. Thus the metes and bound of the claim cannot be determined.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 15-21 and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andrieux et al (Genes dev. 2002 Sep 15; 16(18):2350-64) cited in the IDS in view of Nicolaou et al. (WO99/67252) cited in the IDS.

The instant claims are drawn to a method of treating neuronal connectivity defects comprising administering to an individual in need thereof a therapeutic effective amount of epothilones and salt thereof

As to claim 15 and 16, Andrieux et al teaches that a method of treating schizophrenia administering a therapeutic effective amount of neuroleptics in mice). Andrieux demonstrates neurons contain abundant stable microtubules that are important in for the generation and maintenance of neuronal morphology and functions (page 2350, second paragraph). Andrieux discloses microtubule stabilizer can have a beneficial effect on synaptic function and behavior, suggesting new possibilities for treatment of schizophrenia (abstract). Neuronal connectivity defect refers to mental diseases involve neuronal connectivity disorder in the absence of degenerative anomaly, such as schizophrenia.

Schizophrenia is a specie of a psychiatric disorder as disclosed in applicant's specification (page 4, lines 1-15).

Andrieux did not teach epothilones and a salt thereof to treat or alleviate schizophrenia. The mice in Andrieux, as models for schizophrenia would be individuals in need of treatment of schizophrenia.

As to claims 17-21, Nicolaou et al teaches epothilones analogs and salts thereof and their synthesis for the treatment of one or more chemotherapeutics. Nicolaou further teaches epothilones A, B, C, D and E which are taxol related promoted the polymerization of α and β subunits and possess microtubule depolymeriztion inhibiting activity and are useful against proliferative diseases and read on claims 17, 18 and 19 (page 1 and page 2 bridging).

As to claims 23 and 24, Nicolaou teaches the pharmaceutical composition including can be formulated using solid or liquid vehicles, diluents and additives and the compounds are administered in a dosage range of about 0.05 to 100 g/kg/dose (page 13, lines 4-13).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute epothilones and salts thereof as neuroleptics in the STOP study of Andrieux giving the methods of the instant claims, because Andrieux suggests that microtubule stabilizer can have a

beneficial effect on synaptic function and behavior for the treatment of schizophrenia.

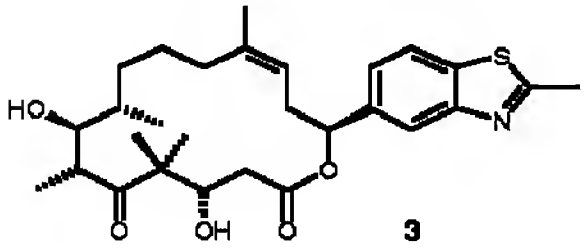
One of ordinary skill in the art would have been motivated to do so with reasonable expectation of success because Nicolaou strongly teaches that an inherent property of epothilones have high levels of microtubule stabilizing effects, i.e. microtubuli depolymerzation inhibiting activity (page 2, first paragraph), and applicants also acknowledges in the specification that their invention derives from the discovery that epothilones can alleviate schizophrenia-related behavioural disorders in an animal model termed STOP deficient mice.

On would have been motivated to combine the references to treat neuronal connectivity defects such as schizophrenia, as epothilones are well known microtubules stabilizers whose pharmacological action is to inhibit depolymeriztion of microtubules.

Claims 15 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andrieux et al (Genes dev. 2002 Sep 15; 16(18):2350-64) cited in the IDS in view of End et al. (Fourth International Electronic conference on Synthetic Organic chemistry) cited in 892 form.

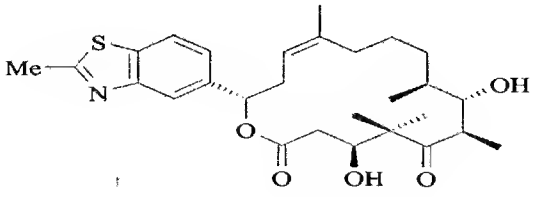
Andrieux' teaching has been discussed *supra*. In addition, Andrieux fails to teach synthetic epothilones of the formula of claims 22 to treat neuronal connectivity defect in an individual.

As to claim 22, End et al teaches synthetic epothilone analogs with improved pharmacological profile including epothilone of formula 3, a taxol-related compound with the ability to inhibit microtubule depolymeration (page 1, introduction and page 3, formula 3).



3

This compound is the same as the claimed compound, because if it is flipped, all the bonds will point in the same direction as in claimed compound; see structure of the claimed compound below;



Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use epothilones and salts thereof as neuroleptics in the STOP study of Andrieux, because Andrieux suggests that

microtubule stabilizer can have a beneficial effect on synaptic function and behavior for the treatment of schizophrenia.

One of ordinary skill in the art would have been motivated to do so with reasonable expectation of success because Nicolaou strongly teaches that an inherent property of epothilones have high levels of microtubule stabilizing effects, i.e. microtubuli depolymerzation inhibiting activity (page 2, first paragraph), and applicants also acknowledges in the specification that their invention derives from the discovery that epothilones can alleviate schizophreniarel-related behavioural disorders in an animal model termed STOP deficient mice.

On would have been motivated to combine the references to treat neuronal connectivity defects such as schizophrenia, as epolhilones are well known microtubules stabilizers whose pharmacological action is to inhibit depolymeriztion of microtubules.

In conclusion

8. No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JEAN CORNET whose telephone number is

(571)270-7669. The examiner can normally be reached on Monday-Friday 7.30am-5.00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JC/

/Patrick J. Nolan/
Supervisory Patent Examiner, Art Unit 4121